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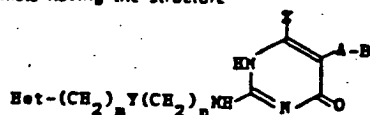
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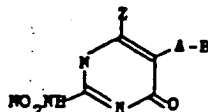
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(57) Process for preparing 2-aminopyrimidones, intermediate 2-nitroaminopyrimidones and a process for their preparation.

(57) 2-Aminopyrimidones which are histamine H₂-antagonists having the structure



in which Het is a nitrogen-containing 5- or 6-membered fully unsaturated heterocyclic group, m is 0 or 1, Y is methylene, oxygen or sulphur, n is 2 or 3, Z is hydrogen or lower alkyl, A is an alkylene group or an alkylene group interrupted by oxygen or sulphur, and B is hydrogen or a methyl, cycloalkyl, heteroaryl, phenyl, naphthyl, benzodioxolyl or dihydrobenzodioxinyl group, are prepared by a process in which an amine $\text{Het}-(\text{CH}_2)_m-\text{Y}(\text{CH}_2)_n-\text{NH}_2$ is reacted with a 2-nitroaminopyrimidone of structure



The new 2-nitroaminopyrimidone intermediates are prepared by reacting nitroguanidine with an oxoester $\text{RO}_2\text{C}-\text{CH}(\text{COZ})-\text{A-B}$ where R is lower alkyl.

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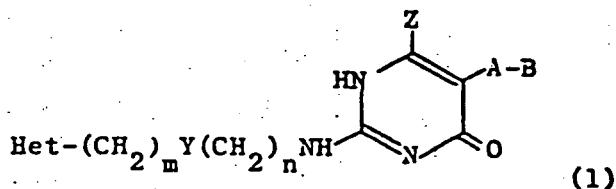
PROCESS FOR PREPARING 2-AMINOPYRIMIDONES,
INTERMEDIATE 2-NITHOAMINOPYRIMIDONES AND
A PROCESS FOR THEIR PREPARATION

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This invention relates to a chemical process for preparing 2-aminopyrimidones which have histamine H₂-antagonist activity, and to novel intermediates for use in
5 this process and to a process for preparing them.

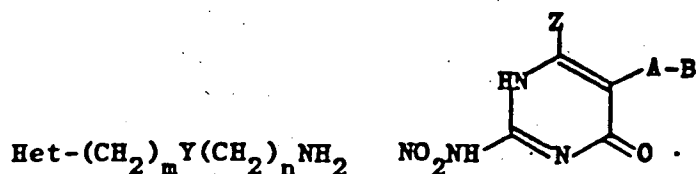
In German Offenlegungsschriften 2643670 and 2658267 there are described specific processes for preparing 2-aminopyrimidones which comprise reacting an amine with a pyrimidone which has a lower alkylthio, benzylthio or
10 halogen group in the 2-position. We have found that a better process for preparing these 2-aminopyrimidones is to react an amine with a pyrimidone which has a nitroamino group in the 2-position.

According to the invention there is provided a process
15 for preparing a 2-aminopyrimidone of Structure 1:-



in which Het is a nitrogen-containing 5- or 6- membered
20 fully unsaturated heterocyclic group which is optionally substituted by one or more lower alkyl, trifluoromethyl, halogen, hydroxy, lower alkoxy or amino groups which groups can be the same or different, m is 0 or 1, Y is methylene, oxygen or sulphur, n is 2 or 3; Z is hydrogen
25 or lower alkyl (preferably methyl); A is C₁-C₅ alkylene or -(CH₂)_p-W-(CH₂)_q- where W is oxygen or sulphur and the sum of p and q is 1 to 4 and B is hydrogen, methyl, C₃-C₆ cycloalkyl, a heteroaryl group optionally substituted by one or more (which may be the same or
30 different) lower alkyl or lower alkoxy groups, or B is a

- 1 naphthyl, 5- or 6-(2,3-dihydro-1,4-benzodioxinyl), or a 4- or
 5-(1,3-benzodioxolyl) group, or a phenyl group optionally
 substituted with one or more (which may be the same or
 different) lower alkyl, lower alkoxy, halogen, aryl(lower
 5 alkoxy) (preferably benzyloxy), hydroxy, lower alkoxy-
 lower alkoxy, trifluoromethyl, di(lower alkyl)amino, phenoxy,
 halophenoxy, lower alkoxyphenoxy, phenyl, halophenyl or
 lower alkoxyphenyl groups; characterised in that an amine
 of Structure 2, in which Het, m, Y and n are as defined
 10 for Structure 1, is reacted with a 2-nitroaminopyrimidone
 of Structure 3, in which Z, A and B are



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as defined for Structure 1. A phenolic hydroxy group can, if
 desired, be protected during the reaction and subsequently
 regenerated. Examples of hydroxy protecting groups are
 methoxymethyl, methylthiomethyl, tetrahydropyranyl, benzyl,
 acyl and lower alkyl.

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Throughout this specification by the terms 'lower
 alkyl' and 'lower alkoxy' are meant alkyl and alkoxy groups
 which can be straight or branched and which contain 1 to 4
 carbon atoms. Particular lower alkyl groups are methyl,
 ethyl, 1-propyl and 2-propyl. Particular lower alkoxy groups
 are methoxy, ethoxy, 1-propoxy and 2-propoxy.

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Examples of heterocycles of the group Het are imidazole,
 pyridine, thiazole, isothiazole, oxazole, isoxazole, triazole
 and thiadiazole. Preferably the group Het is linked to
 $(\text{CH}_2)_m$ by a carbon atom of the heterocycle adjacent to a

- 1 nitrogen atom. Examples of the group Het are 2- or 4-
imidazolyl optionally substituted by lower alkyl
(preferably methyl), halogen (preferably chlorine or
bromine), trifluoromethyl or hydroxymethyl, 2-pyridyl
5 optionally substituted by one or more (which can be the
same or different) lower alkyl (preferably methyl), lower
alkoxy (preferably methoxy), halogen (preferably chlorine
or bromine), amino or hydroxy groups, 2-thiazolyl, 3-
isothiazolyl optionally substituted by chlorine or bromine,
10 3-(1,2,5)-thiadiazolyl optionally substituted by chlorine
or bromine, or 2-(5-amino-1,3,4-thiadiazolyl). Particular
Het groups are 5-methyl-4-imidazolyl, 5-bromo-4-imidazolyl,
2-pyridyl, 3-methyl-2-pyridyl, 3-methoxy-2-pyridyl,
3-ethoxy-2-pyridyl, 3,4-dimethoxy-2-pyridyl, 3-fluoro-2-
15 pyridyl, 3-chloro-2-pyridyl, 3-bromo-2-pyridyl, 3-iodo-2-
pyridyl, 3-bromo-4-methyl-2-pyridyl and 2-thiazolyl.

- Examples of heteroaryl groups B are pyridyl, furyl,
thienyl, thiazolyl, oxazolyl, isothiazolyl, imidazolyl,
pyrimidyl, pyrazinyl, pyridazyl, thiadiazolyl, quinolyl,
20 isoquinolyl, 5,6,7,8-tetrahydroquinolyl, 1,3-dioxolopyridyl,
benzimidazolyl and benzthiazolyl. Particular heteroaryl
groups are 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl,
4-pyridyl, 2-thiazolyl, 2-imidazolyl, 2-pyrimidyl,
2-pyrazyl, 3-pyridazyl, 3-quinolyl and 1-isoquinolyl
25 optionally substituted by one or more lower alkyl or lower
alkoxy groups. Specific heteroaryl groups are 2-furyl,
3-pyridyl, 6-methyl-3-pyridyl, 5,6-dimethyl-3-pyridyl,
6-methoxy-3-pyridyl, 2-methoxy-4-pyridyl and 4-methoxy-
2-pyridyl.

- 30 Specific substituted phenyl groups B are 3-chloro-
phenyl, 3,4-dichlorophenyl, 3-methoxyphenyl, 4-methoxy-
phenyl, 3,4-dimethoxyphenyl and 3,4,5-trimethoxyphenyl.

PREPARATION 9

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1 2,3-Dihydro-1,4-benzodioxin-6-carboxaldehyde (m.p. 41-43°,
prepared by reacting 3,4-dihydroxybenzaldehyde with ethane-
disulphonic acid dimethyl ester and potassium hydroxide) was
condensed with monoethyl malonate in pyridine with piperidine
5 as catalyst to give ethyl 3-(6-(2,3-dihydro-1,4-benzodioxinyl)-
acrylate, m.p. 49-53°, which was reduced with hydrogen and
palladium-on-charcoal, and the product was reacted with ethyl
formate and sodium hydride in 1,2-dimethoxyethane to give ethyl
2-formyl-3-[6-(2,3-dihydro-1,4-benzodioxinyl)]propionate as an
10 oil.

PREPARATION 10

A mixture of ethyl 3-(1-naphthyl)propionate (18.01 g)
15 and ethyl formate (8.88 g) was added to a suspension of sodium
hydride (57% dispersion in oil, 4.43 g) in 1,2-dimethoxy-
ethane stirred at 5°, and the mixture was stirred at 5° for
one hour and allowed to warm to room temperature. Water
(300 ml) was added and the mixture was extracted with chloro-
20 form and the residual aqueous phase adjusted to pH 4 with
hydrochloric acid: the mixture was extracted with ether and the
extracts evaporated to give ethyl 2-formyl-3-(1-naphthyl)-
propionate (16.05 g) as an oil.

PREPARATION 11

25 (i) A solution of sodium methoxide (from 0.535 g sodium)
in dry methanol (40 ml) was added dropwise to a stirred
suspension of 3-fluoro-2-methyl-4-nitro-pyridine N-oxide (2 g)
30 in dry methanol (50 ml) and the mixture was stirred overnight.
Additional sodium methoxide (from 0.653 g sodium) was added
and the mixture was heated under reflux for 1 hour. The
mixture was neutralised with hydrochloric acid and evaporated
to dryness. The residue was extracted with chloroform and
35 the extract was evaporated to dryness to give 3,4-dimethoxy-
2-methylpyridine N-oxide.

1 (ii) Trifluoroacetic anhydride (4.0 ml) was added drop-
wise to a stirred solution of 3,4-dimethoxy-2-methylpyridine
N-oxide (1.91 g) in dichloromethane (25 ml) and the mixture
was left to stand at room temperature for 8 days during which
5 time trifluoroacetic anhydride (4.77 ml) was added in two
portions. The mixture was evaporated to dryness and the
residue was purified by extracting a chloroform solution with
aqueous sodium bicarbonate and elution from silica gel with
10 methanol-chloroform (1:9) to give 2-hydroxymethyl-3,4-dimethoxy-
pyridine (1.6 g).

(iii) 2-Hydroxymethyl-3,4-dimethoxypyridine was reacted
with thionyl chloride in chloroform to give 2-chloromethyl-3,4-
15 dimethoxypyridine hydrochloride, m.p. 158-9° (decomp), which
was reacted with cysteamine hydrochloride and sodium ethoxide
in ethanol to give 2-(3,4-dimethoxy-2-pyridylmethylthio)-
ethylamine.

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EXAMPLE 1

Sodium (1.15 g) was dissolved in methanol (50 ml) and
nitroguanidine (4.7 g) was added to the cooled solution. The
mixture was heated under reflux for 45 minutes, ethyl 2-formyl-
25 3-(3-pyridyl)propionate (9.3 g) was added portionwise and the
mixture was heated under reflux for 45 hours and evaporated to
dryness. Water was added to the residue and the mixture was
extracted with chloroform. The residual aqueous phase was
adjusted to pH 5 with acetic acid, and the solid which was
precipitated was filtered off, washed and dried to give 2-
30 nitroamino-5-(3-pyridylmethyl)-4-pyrimidone, m.p. 214.5-216°,
in 38% yield.

EXAMPLE 2

35 A solution of ethyl 2-formyl-3-(6-methyl-3-pyridyl)-
propionate (1.55 g) in methanol (20 ml) was added to a
stirred solution of sodium methoxide (from 0.161 g sodium) in
methanol (20 ml). Dried nitroguanidine (0.73 g) was added
and the mixture was heated under reflux overnight and evaporated